

A SPECIAL MEETING REVIEW EDITION

Highlights in CAR T-Cell Therapy in Lymphoma From the 60th American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

Special Reporting on:

- 2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma
- Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real-World Experience
- Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance, and Toxicity
- Phase I/II Trial of Multi-Target Chimeric Antigen Receptor Modified T Cells (4SCAR2.0) Against Relapsed or Refractory Lymphomas
- Clinical Responses to CAR.CD30-T Cells in Patients With CD30+ Lymphomas Relapsed After Multiple Treatments Including Brentuximab Vedotin
- Safety of Axicabtagene Ciloleucel CD19 CAR T-Cell Therapy in Elderly Patients With Relapsed or Refractory Large B-Cell Lymphoma
- Cytokine Monitoring in R/R DLBCL Patients Treated With Axicabtagene Ciloleucel: Associations With Toxicities and Outcomes
- Outcomes of Patients With Large B-Cell Lymphomas and Progressive Disease Following CD19-Specific CAR T-Cell Therapy

PLUS Meeting Abstract Summaries

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THE PROOF IS IN THE DATA

CAR T BACKED BY PIVOTAL DATA
WITH 2-YEAR POST HOC ANALYSIS

INDICATION

YESCARTA[®] is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA[®] is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA[®]. Do not administer YESCARTA[®] to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA[®], including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA[®]. Provide supportive care and/or corticosteroids as needed.**
- **YESCARTA[®] is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA[®] REMS.**

Important Safety Information continued on adjacent page.

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with \geq Grade 3. Among patients who died after receiving YESCARTA[®], 4 had ongoing CRS at death.

The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA[®]. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA[®]. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA[®]. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA[®] REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA[®] is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA[®] REMS. The required components of the YESCARTA[®] REMS are: Healthcare facilities that dispense and administer YESCARTA[®] must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA[®] infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA[®] are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA[®].

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with \geq Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA[®] should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA[®] infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA[®] infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA[®] infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA[®] infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA[®] treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA[®] treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA[®] infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence \geq 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including **BOXED WARNING**, on the following pages.

Reference: YESCARTA[®] [package insert]. Santa Monica, Kite Pharma, Inc. 2019.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA®
(axicabtagene ciloleuce) suspension for intravenous infusion
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)].
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient [see Dosage and Administration (2.2.3)].

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. *Pre-treatment:* Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA. *Pre-medication:* Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with

replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation [see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO ₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity (b).	Administer tocilizumab (c) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO ₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014, (b) Refer to Table 2 for management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) [see *Adverse Reactions (6)*]. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see *Patient Counseling Information (17)*]. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated [see *Dosage and Administration (2.3)*].

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients

at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly [see *Management of Severe Adverse Reactions (2.3); Neurologic Toxicities*].

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS [see *Boxed Warning and Warnings and Precautions (5.1 and 5.2)*]. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.

- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. *Viral Reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based [see *Clinical Trials (14)*]. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was

43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence \geq 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions ($>$ 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. The most common (\geq 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders	Febrile neutropenia	34	31
Cardiac disorders	Tachycardia	57	2
	Arrhythmia	23	7
Gastrointestinal disorders	Diarrhea	38	4
	Nausea	34	0
	Vomiting	26	1
	Constipation	23	0
	Abdominal pain	14	1
	Dry mouth	11	0
General disorders and administration site conditions	Fever	86	16
	Fatigue	46	3
	Chills	40	0
	Edema	19	1
Immune system disorders	Cytokine release syndrome	94	13
	Hypogammaglobulinemia	15	0
Infections and infestations	Infections-pathogen unspecified	26	16
	Viral infections	16	4
	Bacterial infections	13	9
Investigations	Decreased appetite	44	2
	Weight decreased	16	0
	Dehydration	11	3
Musculoskeletal and connective tissue disorders	Motor dysfunction	19	1
	Pain in extremity	17	2
	Back pain	15	1
	Muscle pain	14	1
	Arthralgia	10	0
Nervous system disorders	Encephalopathy	57	29
	Headache	45	1
	Tremor	31	2
	Dizziness	21	1
	Aphasia	18	6
Psychiatric disorders	Delirium	17	6
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	11
	Cough	30	0
	Dyspnea	19	3
	Pleural effusion	13	2
Renal and urinary disorders	Renal insufficiency	12	5
Vascular disorders	Hypotension	57	15
	Hypertension	15	6
	Thrombosis	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxemia, renal insufficiency, and hypotension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia

(6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in \geq 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%, Thrombocytopenia 58%, Hypophosphatemia 50%, Hyponatremia 19%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Risk Summary:* There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation: *Risk Summary:* There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential: *Pregnancy Testing:* Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. *Contraception:* See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. *Infertility:* There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia [see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion [see Warnings and Precautions (5.2)], Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy [see Warnings and Precautions (5.8)].

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2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma

Axicabtagene ciloleucel is an autologous chimeric antigen receptor (CAR) T-cell therapy directed at the CD19 antigen.¹ The patient's T cells are engineered to express the single-chain extracellular variable domain against CD19, as well as the CD3 ζ and CD28 intracellular domains to enhance T-cell activation. Axicabtagene ciloleucel is approved in the United States for the treatment of relapsed or refractory large B-cell lymphoma in patients who have received at least 2 prior systemic therapies.² The multicenter, single-arm phase 1/2 ZUMA-1 trial (Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma) evaluated axicabtagene ciloleucel in patients with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma. Eligible patients had not responded to their most recent chemotherapy regimen or had relapsed

within 12 months after undergoing an autologous stem cell transplant. Patients had received prior treatment with an anti-CD20 monoclonal antibody and an anthracycline. Enrolled patients initially received treatment with a conditioning regimen consisting of daily cyclophosphamide (500 mg/m²) plus fludarabine (30 mg/m²) for 3 days. Patients then received axicabtagene ciloleucel with a target dose of 2×10^6 CAR T cells/kg. The primary endpoint was the objective response rate (ORR).

The ZUMA-1 study enrolled 108 patients in the phase 1 and phase 2 portions of the trial.³ The patients' median age was 58 years (range, 23-76 years), one-fourth were ages 65 years or older, and 68% were male. An Eastern Cooperative Oncology Group (ECOG) performance status of 1 was reported in 57% of patients, and 83% had stage III/IV disease. Forty-four percent of patients had an International Prognostic Index (IPI)

score of 3 or 4, and 70% of patients had received 3 or more prior therapies. Seventy-four percent of patients were refractory to a second-line or later line of therapy, 65% had progressive disease as their best response to their most recent treatment, and 23% had relapsed after autologous stem cell transplant. After a median of 15.4 months of follow-up, the ORR was 82%, with a complete response (CR) rate of 54%. The ongoing response rate was 42%. In the initial analysis, adverse events (AEs) that occurred beyond 6 months were generally manageable infections. There were no reports of late-onset treatment-related cytokine release syndrome or neurologic events.

An analysis presented at the 60th American Society of Hematology annual meeting provided long-term data. After a median of 27.1 months of follow-up, 39% of patients had an ongoing response according to investigator assessment.⁴ CRs were seen in 37%. Among the patients who had an initial response at 12 months, 93% had an ongoing response at 24 months. A concordance of 81% was observed between investigator assessment and central review of response. In the phase 2 trial, 33 patients had double-expressor or high-grade B-cell lymphoma. These patients initially had a 91% ORR, including a CR rate of 70%. With the longer follow-up, 48% of these patients showed an ongoing response, all of which were CRs. Among the 39 patients overall who had an ongoing response, 2 (5%) underwent allogeneic stem cell transplant. (No patients underwent an autologous stem cell transplant.) Among patients in the overall study population, the investigator-assessed median duration of response was 11.1

ABSTRACT SUMMARY Late Effects of CD19-Targeted CAR T-Cell Therapy

Long-term toxicity was retrospectively evaluated in 60 patients with relapsed or refractory aggressive non-Hodgkin lymphoma or chronic lymphocytic leukemia who received anti-CD19 CAR T-cell therapy as part of a phase 1/2 clinical trial (Abstract 223). Enrolled patients had survived at least 1 year after treatment. Late AEs were defined as those that persisted beyond 90 days after CAR T-cell infusion. Among 43 patients with non-Hodgkin lymphoma and 17 with chronic lymphocytic leukemia, the CR rate was 48% and the PR rate was 35%. After a median follow-up of 25 months (range, 12.6-62.6 months), 47 patients (78%) were alive. Among 19 evaluable patients with an ongoing CR, 3 (16%) developed significant late cytopenias. Among 48 evaluated patients, 29 (60%) had late hypogammaglobulinemia, including 10 with an ongoing CR. In the entire population, 10 patients (17%) developed a secondary malignancy, 7 (12%) experienced late immune-related events, and 3 (5%) developed late neurologic and psychiatric events. Graft-vs-host disease occurred in 1 of 9 evaluable patients (11%).

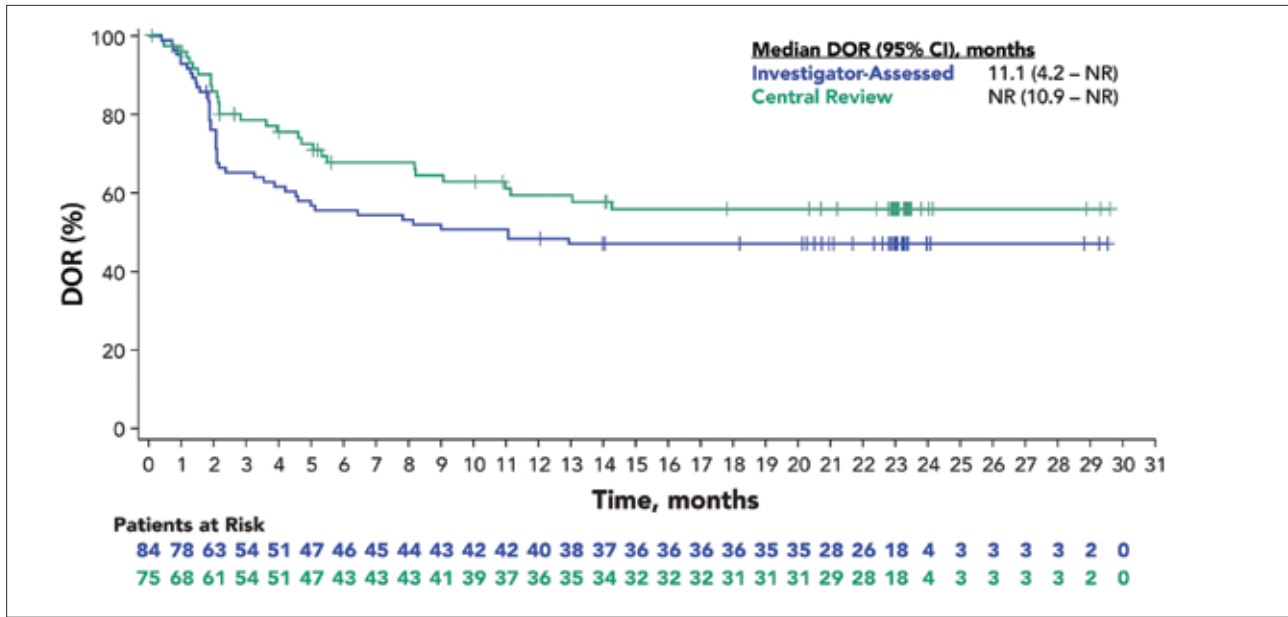


Figure 1. The median duration of response according to investigator assessment in the ZUMA-1 trial of axicabtagene ciloleucel. DOR, duration of response; NR, not reached; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Neelapu SS et al. ASH abstract 2967. *Blood*. 2018;132(suppl 1).⁴

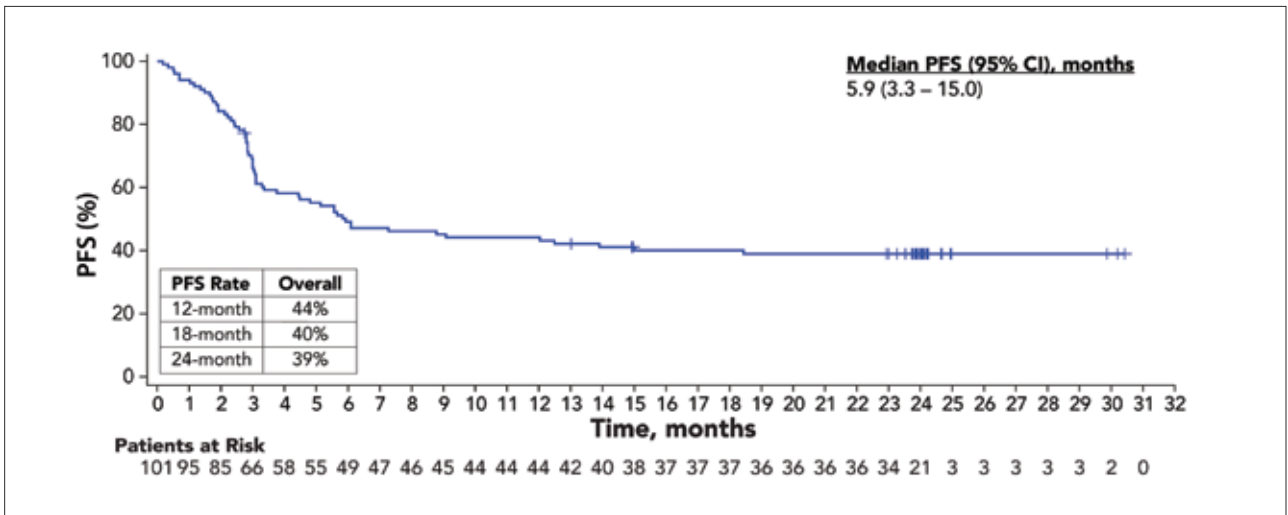


Figure 2. Median progression-free survival according to investigator assessment in the ZUMA-1 trial of axicabtagene ciloleucel. PFS, progression-free survival; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Neelapu SS et al. ASH abstract 2967. *Blood*. 2018;132(suppl 1).⁴

months (95% CI, 4.2 months to not reached; Figure 1), the median progression-free survival (PFS) was 5.9 months (95% CI, 3.3-15.0 months; Figure 2), and the median overall survival was not reached (95% CI, 12.8 months to not reached). Among

32 patients with an ongoing response at 24 months, 21 (66%) had detectable, gene-marked CAR T cells in the peripheral blood.

There were no reports of late-onset cytokine release syndrome, neurologic events, or death. The most frequent

AEs of grade 3 or higher were cytopenias. Cytopenias present at month 3 or afterward included neutropenia (11%), thrombocytopenia (7%), and anemia (3%). All late-onset serious AEs were unrelated to treatment with axicabtagene ciloleucel, and all of these

AEs resolved, with the exception of 1 case of myelodysplastic syndrome. One patient developed 2 incidents of grade 2 infection that were considered related to treatment with axicabtagene ciloleucel.

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ABSTRACT SUMMARY End of Phase 1 Results From ZUMA-6: Axicabtagene Ciloleucel Combination With Atezolizumab for the Treatment of Patients With Refractory Diffuse Large B-Cell Lymphoma

The ZUMA-6 trial (Safety and Efficacy of KTE-C19 in Combination With Atezolizumab in Adults With Refractory Diffuse Large B-Cell Lymphoma [DLBCL]) examined axicabtagene ciloleucel plus atezolizumab in patients with refractory DLBCL (Abstract 4192). The phase 1 portion of the trial used a 3 + 3 design to measure the incidence of dose-limiting toxicities. The 12 patients in the 3 dose cohorts had a median follow-up of 10.4 months (range, 3.1-18.3 months). The ORR was 92%. A treatment-emergent AE of grade 3 or higher occurred in 92% of patients. The most common treatment-emergent AEs of grade 3 or higher were anemia (75%), neutropenia (67%), and encephalopathy (42%). Cytokine release syndrome of grade 3 or higher was observed in 25% of patients, and neurologic AEs of grade 3 or higher occurred in 50% of patients. No grade 5 AEs occurred. One patient in the expansion cohort experienced a dose-limiting toxicity of grade 4 thrombocytopenia and neutropenia lasting longer than 30 days.

Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real-World Experience

A retrospective analysis evaluated real-world outcomes in patients who received axicabtagene ciloleucel as the standard of care at 17 academic centers in the United States.¹ All patients had undergone leukapheresis as of August 31, 2018, and the study included all patients for whom axicabtagene ciloleucel manufacture was intended. There were 295 patients in the intention-to-treat population and 274 patients in the modified intention-to-treat population. Among 295 patients who underwent leukapheresis by the cutoff date, 274 received 3 days of conditioning with daily cyclophosphamide (500 mg/m²) plus fludarabine (30 mg/m²) followed by infusion of the CAR T-cell product. The product did not meet specifications for 7 patients, 12 patients died from causes secondary to lymphoma, 1 patient had nonmeasurable disease, and 1 patient was removed from the study after developing an infection.

The median time from leukapheresis to the start of conditioning therapy was 21.5 days. Bridging therapy was administered to 158 patients, and consisted of chemotherapy (58%), corticosteroids (24%), irradiation (13%), and other regimens (7%). The median follow-up was 3.9 months.

Among the 274 patients in the modified intention-to-treat population, the median age was 60 years (range, 1-83 years), and 33% were ages 65 years or older. The B-cell lymphoma subtype was DLBCL in 68%, transformed follicular lymphoma in 26%, and PMBCL in 6%. Eighty-one percent of patients had an ECOG performance status of 0 or 1, and 81% of patients had stage III/IV disease. The IPI score was 3 or higher in 55% of patients. Three-fourths of patients had received 4 or more prior lines of therapy. One hundred patients had primary refractory disease, and 121 were refractory to their second or later

line of treatment. Ninety-five patients (33%) had relapsed after autologous stem cell transplant.

Patients in the real-world population were slightly younger than those in the ZUMA-1 trial.² The median age was 58 years vs 60 years. The proportion of patients ages 65 years or older was 25% vs 33%. In the ZUMA-1 trial, all patients had an ECOG performance status of 0 or 1. In the real-world analysis, the ECOG performance status was 0 or 1 in 81%, 2 in 15%, and 3 or 4 in 4%. In ZUMA-1, 83% of patients had stage III/IV disease. ZUMA-1 included lower proportions of patients with an IPI score of 3 or higher (44% vs 55%), patients who had received 4 or more prior therapies (70% vs 75%), and patients who had relapsed following autologous stem cell transplant (23% vs 33%). The ZUMA-1 trial included patients with DLBCL (76%), transformed follicular lymphoma (15%), and PMBCL (7%).

In the real-world study, 253 evaluable patients had DLBCL, including 151 (60%) with germinal center B-cell-like DLBCL and 102 (40%) with activated B-cell-like DLBCL. Among 272 patients with available genetic data, fluorescence in situ hybridization identified double-hit or triple-hit genetics in 23% and double-expressor genetics in 38%.

The real-world study included 124 patients (43%) who would not have met the eligibility requirements of the ZUMA-1 trial at the time of leukapheresis. Criteria that would have led to exclusion from ZUMA-1 included low platelet levels (13%), active deep vein thrombosis or pulmonary embolism (9%), prior anti-CD19 or CAR T-cell therapy (8%), inadequate glomerular filtration (8%), history of lymphoma in the central nervous system (8%), symptomatic pleural effusion (4%), inadequate ejection fraction (4%), and prior allogeneic stem cell transplant (2%).

In the real-world analysis, the median follow-up was 3.9 months. The best ORR at day 90 was 81%, including a CR rate of 57%. Covariates associated with an increased likelihood of an ongoing CR at 90 days included female sex ($P=.009$), an ECOG performance status of 0 or 1 ($P=.024$), relapsed disease ($P=.011$), nonbulky disease ($P=.040$), and meeting the eligibility requirements for ZUMA-1 ($P=.037$). The median PFS was 6.18 months (95% CI, 4.57 months to not reached; Figure 3), and the estimated 6-month overall survival was 72% (95% CI, 65%-80%).

Rates of any-grade cytokine release syndrome were similar in the real-world study and the clinical trial (92% vs 93%; Table 1). Grade 3 or higher cytokine release syndrome occurred in 7% vs 13%. The median time to onset of cytokine release syndrome was 3 days vs 2 days. Neurotoxicity of any grade was observed in similar proportions of patients (69% vs 65%), as was neurotoxicity of grade 3 or higher (33% vs 31%). The median time to

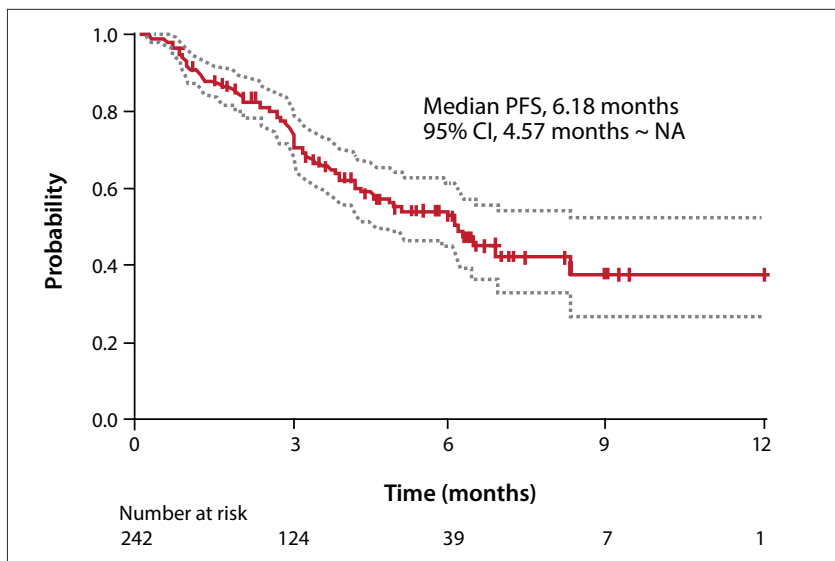


Figure 3. Median progression-free survival in a real-world analysis of patients with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel. PFS, progression-free survival. Adapted from Nastoupil LJ et al. ASH abstract 91. *Blood*. 2018;132(suppl 1).¹

Table 1. Safety of Axicabtagene Ciloleucel in a Real-World Analysis and ZUMA-1

	Standard-of-Care Axicabtagene Ciloleucel N=274 (mITT)	ZUMA-1 ² N=108
All grades of cytokine release syndrome, ^a n (%)	240 (92)	100 (93)
Grade ≥ 3 cytokine release syndrome, n (%)	18 (7)	14 (13)
Median time to onset of cytokine release syndrome	3 days	2 days
All grades of neurotoxicity, ^b n (%)	181 (69)	70 (65)
Grade ≥ 3 neurotoxicity, n (%)	85 (33)	33 (31)
Median time to onset of neurotoxicity	6 days	5 days

^aThe Lee criteria were used for grading cytokine release syndrome.

^bCriteria from Common Terminology Criteria for Adverse Events (CTCAE) or CAR T-Cell Therapy-Associated Toxicity Working Group (CARTOX) were used for grading neurotoxicity.

mITT, modified intention-to-treat; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma.

Data from Nastoupil LJ et al. ASH abstract 91. *Blood*. 2018;132(suppl 1).¹

onset of neurotoxicity was also similar (6 vs 5 days). Patients in the real-world study were more likely to have received tocilizumab (63% vs 45%) or corticosteroids (55% vs 29%). However, the studies had similar rates of grade 5 AEs (3%-4%) and treatment-related deaths (1%-2%).

References

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Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance, and Toxicity

Another multicenter, retrospective study assessed the real-world efficacy and toxicity outcomes following axicabtagene ciloleucel treatment.¹ The study also evaluated patient characteristics, use of bridging therapy, and biomarkers to predict response or toxicity. The study enrolled patients who were treated with commercially available axicabtagene ciloleucel from December 2017 through October 2018 at 6 academic medical centers in the United States. Patient selection, supportive care, assessment of toxicity and response, and toxicity management were performed according to institutional practice. Bridging therapy was used at the discretion of the treating physician. Serial peripheral blood samples

were taken between days 0 and 28 from 4 patients with a response and 4 without a response. Frozen peripheral blood mononuclear cells were then evaluated by single-cell mass cytometry using a panel of 38 metal-tagged monoclonal antibodies. Serial biopsies from 2 patients with primary disease resistance were evaluated by multiplex immunofluorescence and standard immunohistochemistry.

The analysis included 104 patients, and 60% would not have qualified for enrollment in the ZUMA-1 trial.² The patients' median age was 63.8 years (range, 21-80 years). Disease subtypes included DLBCL (43%), high-grade B-cell lymphoma (15%), and PMBCL (6%). The ECOG performance status

was 0 or 1 in 90%, and the IPI score was 3 to 5 in 46%. Genetic analysis showed that 20% of patients were double hit and 4% were triple hit. A prior autologous stem cell transplant was reported in 27% of patients, and 3% had undergone allogeneic stem cell transplant. Ninety-one percent of patients were refractory to their most recent therapy. Forty percent of patients received bridging therapy.

Thirteen patients (11%) underwent leukapheresis but never received the axicabtagene ciloleucel infusion. Among these patients, 6 had progressive disease, 2 had an infection, 1 had a CR after bridging therapy, and 1 had another malignancy. In 3 patients, the axicabtagene ciloleucel product could not be manufactured to specification.

After a median follow-up of 5.6 months, the best ORR in 95 patients was 71%. Among the intention-to-treat population, the ORR was 62%. The ORR at 6 months in 51 evaluable patients was 43%. The median duration of response was 4.9 months (95% CI, 4.9 months to not reached; Figure 4). The median PFS was 5.6 months (95% CI, 2.9 months to not reached; Figure 5). The median overall survival was not reached.

Cytokine release syndrome of any grade occurred in 94% of patients, and was grade 3 or higher in 16%. The median time to onset of cytokine release syndrome was 1 day (range, 0-14 days), and the median duration was 6 days (range, 1-27 days). Neurotoxicity of any grade was observed in 76% of patients, including 39% with neurotoxicity of grade 3 or higher. The median time to onset of neurotoxicity was 5 days (range, 0-34 days), and the median duration was 8 days (range, 1-52 days). Tocilizumab was administered to 67% of patients and corticosteroids to 64%.

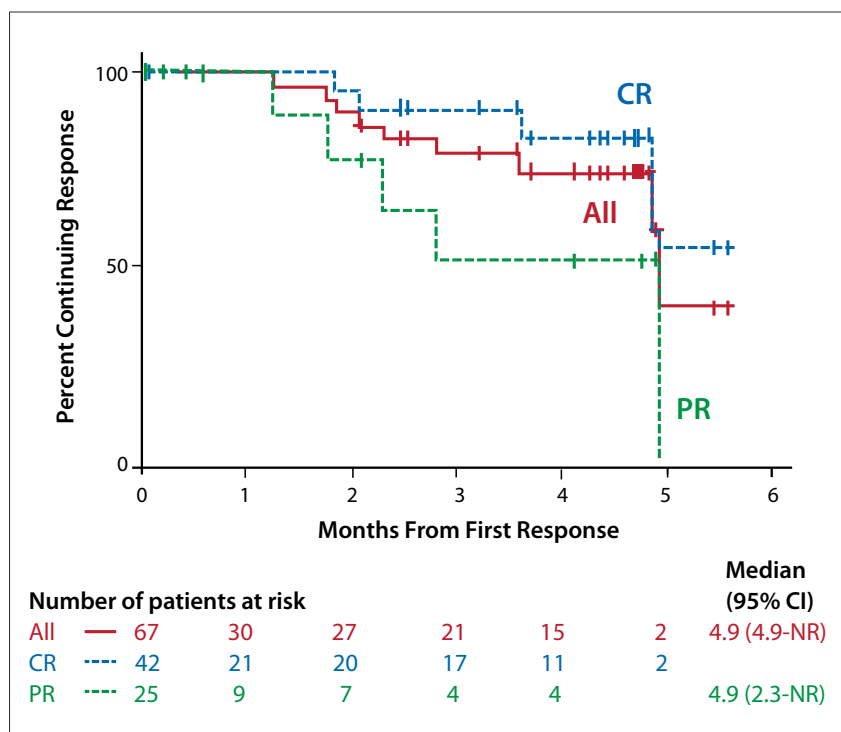


Figure 4. The median duration of response in a real-world analysis of patients with lymphoma treated with axicabtagene ciloleucel. CR, complete response; NR, not reached; PR, partial response. Adapted from Jacobson CA et al. ASH abstract 92. *Blood*. 2018;132(suppl 1).¹

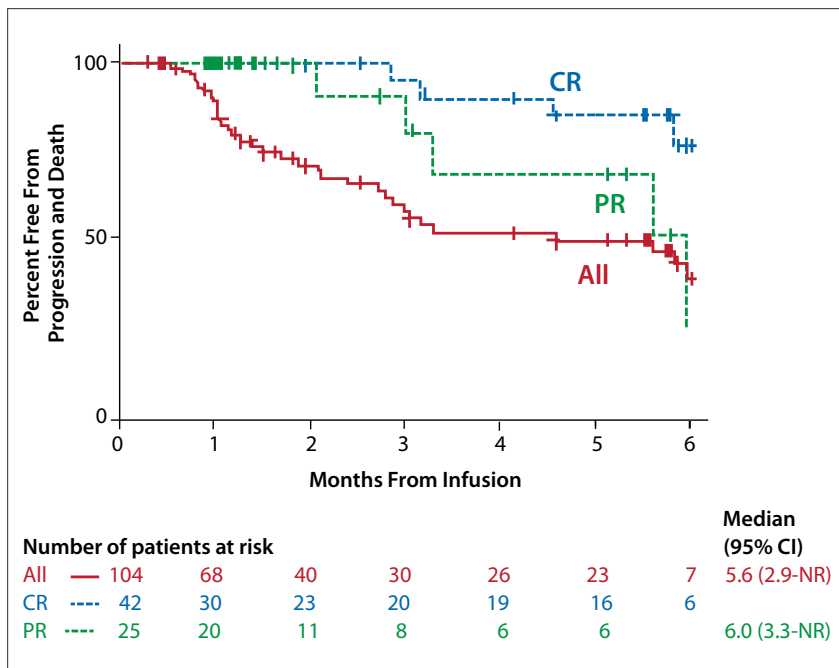


Figure 5. Median progression-free survival in a real-world analysis of patients with lymphoma treated with axicabtagene ciloleucel. CR, complete response; NR, not reached; PR, partial response. Adapted from Jacobson CA et al. *ASH abstract 92. Blood.* 2018;132(suppl 1).¹

ABSTRACT SUMMARY A Phase I First-in-Human Clinical Trial of CD19-Targeted 19-28z/4-1BBL “Armored” CAR T Cells in Patients With Relapsed or Refractory NHL and CLL Including Richter’s Transformation

A phase 1 trial evaluated escalating doses of autologous 19-28z/4-1BBL CAR T cells (Abstract 224). Eligible patients had relapsed or refractory chronic lymphocytic leukemia, DLBCL, indolent non-Hodgkin lymphoma, or acute B-cell lymphoblastic leukemia. Twenty-nine patients received the CAR T-cell infusion. The median follow-up was 4.8 months (range, 1-12.3 months). Twenty patients received the maximum dose of 3×10^6 CAR T cells/kg. A CR was reported in 15 patients (54%), and a PR in 8 (29%). CAR T cells showed maximum expansion between days 7 and 14 after infusion, and were detected in the peripheral blood beyond 6 months after the infusion. No patient developed severe cytokine release syndrome. Three patients (6%) developed grade 3 neurotoxicity. There were no reports of grade 4/5 neurotoxicities or cerebral edema.

Half of patients with an initial PR developed a CR with longer follow-up. Nonrelapse mortality was 7%, and consisted of cytokine release syndrome, infection, and cardiac

events, all occurring in 2 patients each, and neurotoxicity in 1 patient. Thirty percent of patients were transferred to the intensive care unit, and 19% were readmitted.

According to univariate analysis, inferior outcomes were associated with an ECOG performance status of 2, 3, or 4 and increased tumor bulk. Biomarkers associated with a higher likelihood of response included a low C-reactive protein (CRP) level at baseline ($P=.004$) and a high absolute lymphocyte count at the time of leukapheresis ($P=.003$). A CRP level of less than 30 mg/L at baseline was significantly associated with response duration, PFS, and overall survival ($P<.05$), and a peak ferritin level of less than 5000 ng/mL was significantly associated with PFS and overall survival ($P<.05$). A significant correlation was observed between a high peak CRP level and high-grade neurotoxicity ($P=.009$) and between a high peak ferritin level and high-grade neurotoxicity or cytokine release syndrome ($P<.001$).

In the overall study population, the populations of CD4-positive and CD8-positive CAR T cells peaked at day 7. In patients with a response to axicabtagene ciloleucel, markers of T-cell activation, such as Ki67, were upregulated in both CAR-positive and CAR-negative T cells.

The 2 patients with primary refractory disease had different mechanisms of resistance. Biopsies from patient 1 at day 37 after treatment showed no CD19 expression and high expression levels of programmed cell death ligand 1 (PD-L1), both of which would protect tumor cells from axicabtagene ciloleucel. Biopsies from patient 2 taken at day 58 after treatment were CD19-positive and PD-L1-negative; however, no CAR T cells were visible.

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Phase I/II Trial of Multi-Target Chimeric Antigen Receptor Modified T Cells (4SCAR2.0) Against Relapsed or Refractory Lymphomas

CAR T-cell therapy has induced high CR rates in many studies of patients with hematologic malignancies.¹ However, the technology is still relatively new, and modifications to CAR T-cell products could improve patient outcomes. A fourth-generation CAR T-cell product, 4SCAR, was designed to improve safety compared with earlier generations.² In addition to a tumor-targeting single-chain variable fragment region, the 4SCAR product includes regions for antigen cosignaling, T-cell activation and survival, and a safety switch mediated by inducible caspase-9.

The 4SCAR19 product (CD19-scFv/CD28/CD137/CD27/CD3 ζ -iCasp9) is directed at the CD19 antigen. In a study of children and adults with acute B-cell lymphoblastic leukemia who received conditioning chemotherapy followed by an infusion of 4SCAR19, 87% of patients (96/110) had a CR, including 51 children and 45 adults.² Among 69

patients with a bone marrow blast cell count of less than 50%, 91.3% achieved a CR, while the 33 patients with a blast count of at least 50% had a CR rate of 75.8%. After a median of 115.5 days (range, 0-455 days), 55% of patients relapsed. The median survival was 222 days (range, 23-1041 days). Grade 1/2 cytokine release syndrome was observed in 88% of patients, and grade 3/4 cytokine release syndrome occurred in 12%. Among the patients with cytokine release syndrome, 35% had at least 50% blast cells in the bone marrow. The data show high response rates, regardless of the tumor burden. No significant correlation was observed between the CAR T-cell dose and patient response. Patients with a high tumor burden at baseline tended to relapse more quickly, owing to the tumor's loss of the CD19 antigen and CAR T-cell exhaustion.

The 4SCAR2.0 product was developed to address tumor antigen escape and T-cell exhaustion.³ The

product has been successfully used to develop a CAR T-cell therapy that recognizes CD19 plus another antigen, such as CD20, CD22, CD30, CD38, CD70, or the prostate-specific membrane antigen (PSMA). PSMA is not expressed in normal vasculature, but is highly expressed in numerous tumor types. PSMA is present in a small subset of glial cells, suggesting that agents that target this antigen would be associated with a low level of off-target effects. Among 40 B-cell lymphoma specimens, 98% were positive for PSMA according to immunohistochemistry. Patients can receive several infusions of the 4SCAR2.0 product. A CAR T-cell product with the mouse single-chain variable fragment directed at CD19 can be repetitively infused into the same patient without inducing anti-CAR antibodies. CAR T-cell products directed against different antigens can be infused into the same patient, with simultaneous expansion of both products.

A phase 1/2 study enrolled lymphoma patients with stable or progressive disease who had no further treatment options and a life expectancy exceeding 2 months.³ Biopsies were stained for target antigens, including CD19, CD20, CD22, CD30, CD38, CD70, and PSMA. Among the 18 patients enrolled, 11 had DLBCL, 3 had PMBCL, 3 had follicular lymphoma, and 1 had another B-cell lymphoma subtype. The 4SCAR2.0 product was manufactured to recognize CD19 plus 1 other antigen: CD22 (n=10), CD20 (n=3), CD30 (n=2), CD38 (n=1), CD70 (n=1), or PSMA (n=1). A CR was seen in 10 patients, and a PR in 7. Disease progression occurred in 1 DLBCL patient whose CAR T-cell product was directed at CD19 and CD22. Sequential infusions improved the response rate (Figure 6).

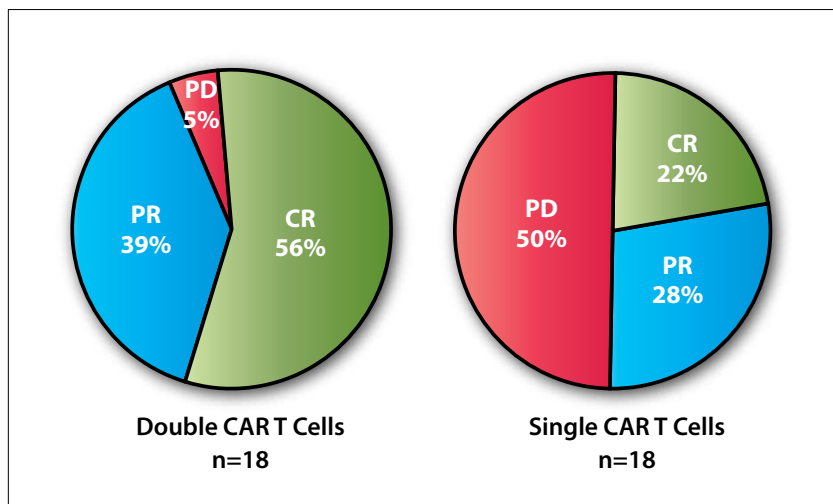


Figure 6. In a phase 1/2 study of multitarget CAR modified T cells, sequential infusions improved the response rate. CAR, chimeric antigen receptor; CR, complete response; PD, progressive disease; PR, partial response. Adapted from Chang LJ et al. ASH abstract 225. *Blood*. 2018;132(suppl 1).³

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Clinical Responses to CAR-CD30-T Cells in Patients With CD30+ Lymphomas Relapsed After Multiple Treatments Including Brentuximab Vedotin

CAR T-cell therapy is limited by the tumor's ability to stop expressing the target antigen and by inherent tumor antigen heterogeneity.¹ To address the need for more versatile targeting, a CAR T-cell therapy targeting CD30 was developed.² CD30 is universally expressed on the cells of Hodgkin lymphoma and anaplastic large-cell lymphoma, and in some patients with other T-cell and B-cell lymphomas.³ CD30 represents an attractive target for Hodgkin lymphoma therapies because it is overexpressed on Hodgkin lymphoma cells and minimally expressed on normal cells. Brentuximab vedotin is an antibody-drug conjugate that targets CD30 and is used to treat patients with CD30-expressing lymphomas.⁴ In a phase 1 dose-escalation study, CD30-directed CAR T-cell therapy without prior lymphodepletion treatment was safe and showed efficacy, with a CR in 1 out of 7 patients with relapsed Hodgkin lymphoma.

A phase 1b/2 study evaluated CD30-directed CAR T-cell therapy (CD30-CAR) after lymphodepletion in patients with CD30-positive Hodgkin or non-Hodgkin lymphoma who required treatment after at least 2 previous lines of therapy.⁵ The phase 1b portion followed a standard 3 + 3 design to test 2 dose levels: 1×10^8 CAR T cells/m² and 2×10^8 CAR T cells/m². Lymphodepletion treatment consisted of bendamustine monotherapy (90 mg/m²) for 2 days

or bendamustine (70 mg/m²) plus fludarabine (30 mg/m²) for 3 days. Patients could receive bridging therapy after leukapheresis. Lymphodepletion therapy began on day 1, followed by infusion of CD30-CAR T cells on days 3 to 6. The trial enrolled 22 patients with classical Hodgkin lymphoma, 1 patient with enteropathy-associated T-cell lymphoma, and 1 patient with Sézary syndrome. The patients' median age was 34.5 years (range, 23-69 years), and they had received a median of 7.5 prior lines of therapy (range, 3-17). Prior therapies included brentuximab vedotin (96%), checkpoint inhibitors (67%), autologous stem cell transplant (71%), and allogeneic stem cell transplant (29%).

Manufacture of CAR-CD30 cells was completed in 25 patients. Eight patients underwent lymphodepletion with bendamustine monotherapy, which improved expansion of CAR-CD30 T cells after infusion compared with no lymphodepletion. All 3 patients treated at the lower dose level of CAR-CD30 T cells had progressive disease at the 6-week assessment. Among 5 patients treated at the higher dose level, 1 patient had stable disease, 1 had progressive disease, and 3 had a CR. However, the latter 3 patients all had a CR after treatment with bridging chemotherapy, prior to the CAR T-cell infusion. The combination of bendamustine plus fludarabine was superior to bendamustine alone in

ABSTRACT SUMMARY CD30-Chimeric Antigen Receptor (CAR) T Cells for Therapy of Hodgkin Lymphoma

A phase 1 trial is investigating CD30-directed CAR T-cell therapy in patients with relapsed or refractory CD30-positive Hodgkin lymphoma (Abstract 680). Preliminary results were reported at the ASH meeting. Fifteen patients will receive cyclophosphamide and fludarabine followed by a single infusion of CD30-directed CAR T cells, with dose escalation from 2×10^7 to 2×10^8 CAR T cells/m². The primary objective is safety. CAR T cells have been manufactured for 22 patients. Culture duration was 15 ± 3 days. The CAR T-cell products consisted of more than 98% T cells, and these were mainly effector T cells. Eleven patients evaluable for safety had a diagnosis of Hodgkin lymphoma and had received a median of 5 prior regimens (range, 2-9). Among 9 patients evaluable for efficacy, a CR occurred in 6. Two of these patients developed progressive disease after the CR. Toxicities included grade 1 cytokine release syndrome, maculopapular rash, transient cytopenias, nausea, and alopecia.

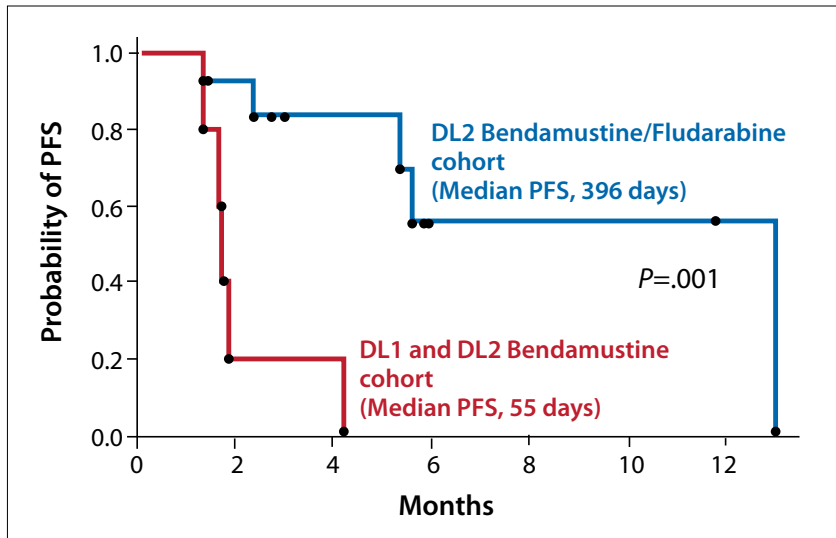


Figure 7. In a phase 1b/2 study, progression-free survival was improved in patients treated with bendamustine plus fludarabine vs bendamustine alone before the infusion of CAR-CD30 T cells. CAR, chimeric antigen receptor; DL, dose level; PFS, progression-free survival. Adapted from Grover NS et al. ASH abstract 681. *Blood*. 2018;132(suppl 1).⁵

ABSTRACT SUMMARY Radiation Therapy as a Bridging Strategy for Refractory Diffuse Large B-Cell Lymphoma Patients Awaiting CART Manufacturing of Axicabtagene Ciloleucel

Nine patients with DLBCL or transformed follicular lymphoma in a case series received radiation treatment as bridging therapy prior to infusion with axicabtagene ciloleucel (Abstract 4220). The goal of radiation treatment was to reduce the tumor burden and to address urgent tumor-related symptoms during the manufacture of CAR T cells. Patients had received a median of 3 prior lines of therapy (range, 2-5). Six patients had double-hit genetics, and 5 had bulky disease. Patients received between 9 Gy and 30 Gy of radiation in up to 10 fractions. The ORR was 75% (6/8) at day 30 and 80% (4/5) at day 90. Grade 3/4 cytokine release syndrome occurred in 1 patient (12.5%), and grade 3/4 CAR T-cell-related encephalopathy syndrome occurred in 3 patients. No severe toxicity was attributed to radiation treatment.

increasing levels of interleukin (IL) 15 ($P=.02$) and IL-7 ($P=.02$), which led to sustained increases in these 2 cytokines for 2 weeks after the CAR T-cell infusion. Sixteen patients received bendamustine plus fludarabine as lymphodepletion therapy. These patients had a CR rate of 75%. Two patients achieved a CR prior to lymphodepletion. Two patients had a PR, 1 had stable disease, and 1 had progressive disease. Patients treated with bendamustine plus fludarabine prior to the infusion of CAR-CD30 T cells had a significantly improved PFS compared with those who received bendamustine monotherapy (396 vs 55 days; $P=.001$; Figure 7).

Three patients developed grade 1/2 cytokine release syndrome. No neurotoxicity was observed in any of the patients who received the CAR-CD30 infusion. A mild rash was observed in 8 patients.

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Safety of Axicabtagene Ciloleucel CD19 CAR T-Cell Therapy in Elderly Patients With Relapsed or Refractory Large B-Cell Lymphoma

In the ZUMA-1 study of axicabtagene ciloleucel, the ORR and rate of ongoing response at 12 months did not significantly differ between patients younger than 65 years vs those 65 years or older.¹

Safety outcomes in these 2 patient populations were not reported. A retrospective analysis evaluated safety and efficacy outcomes in younger vs older patients with relapsed or refractory large B-cell lymphoma

treated with axicabtagene ciloleucel at a single institution.² Patients received conditioning chemotherapy consisting of cyclophosphamide plus fludarabine on days -5 to -3 prior to infusion with axicabtagene ciloleucel.

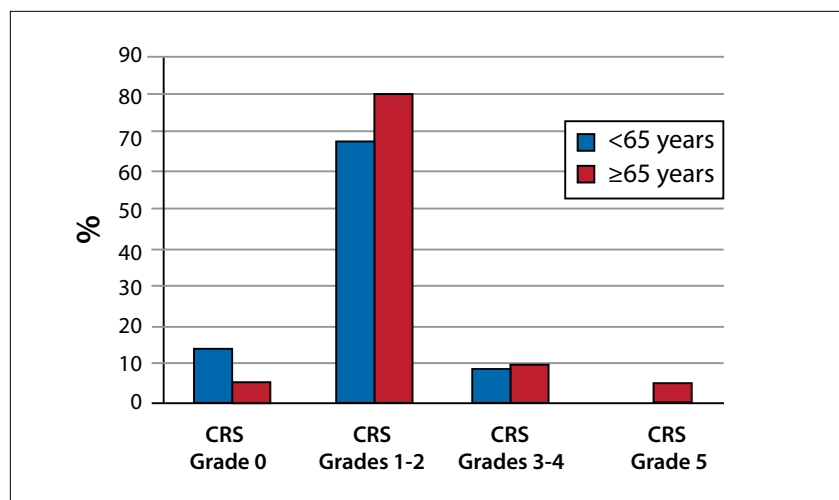


Figure 8. Rates of cytokine release syndrome across all grades were comparable between younger (<65 years) and older (≥65 years) patients treated with axicabtagene ciloleucel in the ZUMA-1 or ZUMA-9 trials. CRS, cytokine release syndrome; ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma; ZUMA-9, Axicabtagene Ciloleucel Expanded Access Study. Adapted from Sano D et al. ASH abstract 96. *Blood*. 2018;132(suppl 1).²

ABSTRACT SUMMARY Sequential Anti-CD19 Directed Chimeric Antigen Receptor Modified T-Cell Therapy (CART19) and PD-1 Blockade With Pembrolizumab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas

A single-institution study prospectively evaluated pembrolizumab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma who progressed after treatment with CD19-directed CAR T-cell therapy (Abstract 4198). Pembrolizumab (200 mg) was administered every 3 weeks for 18 doses, or until disease progression or unacceptable toxicity. Twelve patients received a median of 5 prior therapies (range, 3-8). The median time from CAR T-cell infusion to the first pembrolizumab dose was 3.3 months (range, 0.4-42.8 months). The median PFS after CAR T-cell infusion was 2.8 months (range, 0.3-35.7 months). Among 11 evaluable patients, 9 demonstrated expansion of CAR T cells after the first pembrolizumab cycle. The ORR was 25%, with a CR in 1 patient and a PR in 2 patients. The magnitude of CAR T-cell expansion after administration of pembrolizumab did not correlate with clinical response. Grade 3/4 AEs included grade 3 cytokine release syndrome in 1 patient and grade 4 neutropenia in 3 patients.

The axicabtagene ciloleucel infusion was administered on day 0, with a target dose of 2×10^6 CAR T cells/kg. Enrolled patients had received axicabtagene ciloleucel between June 18, 2015 and September 17, 2018 as the standard of care or through

participation in the ZUMA-1 or ZUMA-9 (Axicabtagene Ciloleucel Expanded Access Study) clinical trials. Patients remained in the hospital and were monitored for toxicities for at least 7 days after administration of the CAR T-cell infusion. Patients

with at least 30 days of follow-up after the axicabtagene ciloleucel infusion were considered evaluable for safety. Cytokine release syndrome and CAR T-cell-related encephalopathy syndrome were graded according to the CAR T-Cell Therapy–Associated Toxicity (CARTOX) system.³ Responses were evaluated based on Lugano 2014 criteria.⁴

All 72 patients included in the study were evaluable for safety, and 67 were evaluable for efficacy. Most patients (n=52) were younger than 65 years. In the cohort of younger patients, the median age was 42 years (range, 23-64 years), 26.9% were female, and 94.2% had an ECOG performance status of 0 to 2. Stage III/IV disease was noted in 80.8% of patients. Disease histologies included DLBCL (59.6%), PMBCL (21.2%), and transformed follicular lymphoma (19.2%). In the cohort of older patients, the median age was 68 years (range, 65-83 years), 25% were female, and 95% had an ECOG performance status of 0 to 2. Stage III/IV disease was present in 90% of patients. Histologic subtypes included DLBCL (80%) and transformed follicular lymphoma (20%). A similar proportion of patients in each arm received axicabtagene ciloleucel treatment as the standard of care (55%-58%). More patients in the older cohort had an IPI score of 3 to 5 (67% vs 85%), and more patients in the younger cohort had received 3 or more prior lines of therapy (79% vs 60%).

At day 30 after infusion with axicabtagene ciloleucel, the ORR was 78% in the younger cohort vs 94% in the older cohort, but this difference was not significant ($P=.1675$). The CR rates were 50% in the younger cohort vs 71% in the older cohort ($P=.2699$). The median overall survival was 15.4 months overall, and was similar for both groups of patients ($P=.27$).

Rates of cytokine release syndrome across all grades were comparable between the younger and older

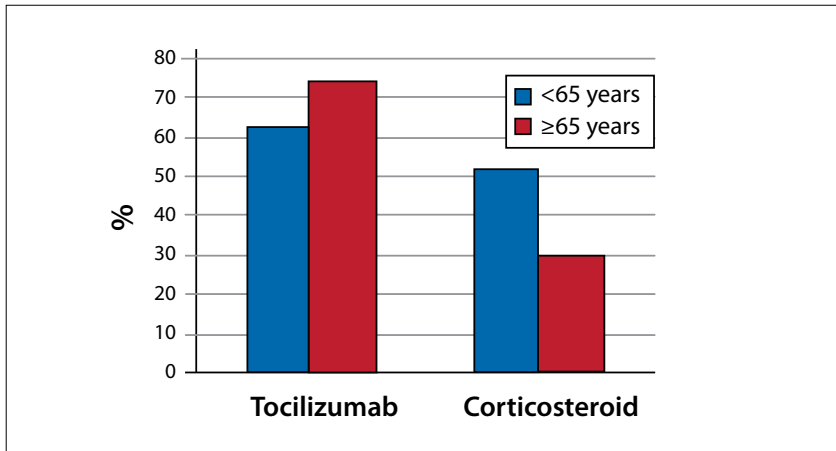


Figure 9. The use of tocilizumab and corticosteroids among younger (<65 years) and older (≥65 years) patients treated with axicabtagene ciloleucel in the ZUMA-1 or ZUMA-9 trials. ZUMA-1, Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma; ZUMA-9, Axicabtagene Ciloleucel Expanded Access Study. Adapted from Sano D et al. ASH abstract 96. *Blood*. 2018;132(suppl 1).²

patients ($P=.18$; Figure 8). Rates of CAR T-cell–related encephalopathy syndrome were also similar across all grades for younger vs older patients ($P=.29$). Tocilizumab was used in 63.5% of the younger patients and in 75.0% of the older patients ($P=.41$).

The use of corticosteroids was more frequent in younger patients, at 52%, vs 30% in older patients ($P=.002$; Figure 9). Patients in both cohorts were hospitalized for a median of 16 days ($P=.62$). Rates of admission to the intensive care unit were 42% in

younger patients vs 35% in older patients ($P=.38$).

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Cytokine Monitoring in R/R DLBCL Patients Treated With Axicabtagene Ciloleucel: Associations With Toxicities and Outcomes

Two commonly observed AEs associated with CAR T-cell therapy are cytokine release syndrome and neurotoxicity—notably, CAR T-cell–related encephalopathy syndrome. Both cytokine release syndrome and CAR T-cell–related encephalopathy syndrome can lead to hospitalization and death. As a result, patients who receive CAR T-cell infusions require vigilant monitoring and prompt treatment of toxicities. Because CAR T-cell therapy induces the expression of numerous cytokines associated with an immune response, identification and monitoring of serum biomarkers could enable earlier

intervention in patients who are likely to develop severe toxicity.

A phase 1 trial investigated the safety and long-term outcomes of CAR T-cell therapy in 53 patients with relapsed or refractory B-cell acute lymphoblastic leukemia.¹ After a median follow-up of 29 months, the CR rate was 83%. After infusion, however, 14 patients (26%) developed severe cytokine release syndrome. One patient died from severe cytokine release syndrome and multiorgan failure. Another 31 patients (58%) developed grade 1/2 cytokine release syndrome. Symptoms of cytokine release syndrome included fever, tachycardia, hypotension, respi-

ratory distress, and hypoxemia. To manage cytokine release syndrome, treatments included supportive care only (42%), tocilizumab plus a glucocorticoid (25%), tocilizumab alone (11%), and glucocorticoids only (8%). Neurologic AEs consisted of confusion, disorientation, aphasia, encephalopathy, and seizure. Neurologic AEs of grade 2, 3, or 4 were observed in 2%, 36%, and 6% of patients, respectively. There were no reports of grade 5 neurotoxicity or cerebral edema.

The relationship between the cytokine levels and CAR T-cell–associated toxicities was evaluated in patients with relapsed or refrac-

tory DLBCL.² To determine which cytokines to monitor, a panel of 38 was retrospectively analyzed in serum samples from 53 patients with acute B-cell lymphoblastic leukemia enrolled in the phase 1 trial discussed above.¹ Cytokine levels were compared in patients who did or did not develop cytokine release syndrome or neurotoxicity requiring treatment. The analysis revealed that, on days 0 to 2, patients with cytokine release syndrome or neurotoxicity requiring intervention had increased levels of several cytokines, including interferon γ and IL-2, IL-6, and IL-15. For the study of patients with DLBCL, levels of these 4 cytokines were examined, as well as those of angiotensin 1 and 2, IL-1 β , and tumor necrosis factor α .² Levels of CRP and ferritin were also evaluated. Serum samples were collected at baseline and on day 0. Samples were also collected daily during hospitalization. Cytokine release syndrome and CAR T-cell-related encephalopathy syndrome were graded daily during hospitalization. The study enrolled 30 patients with relapsed or refractory DLBCL who received treatment with axicabtagene ciloleucel at a single center. After collection, samples were analyzed with a point-of-care device that revealed serum cytokine levels within 90 minutes. Results were validated using a standard multiplex assay. Cytokine release syndrome and CAR T-cell-related encephalopathy syndrome were prospectively graded based on revised criteria.^{3,4}

The median age of the 30 patients was 64 years (range, 47-75 years), and 70% were male. Half had de novo DLBCL, and half had transformed indolent lymphoma. Twenty percent had bulky disease, 90% had Ann Arbor stage III/IV disease, and 80% had an IPI score of 3 or higher at the time of leukapheresis. Sixty percent of patients had received 3 or more lines of therapy prior to study entry. Bridging chemotherapy was used in 67%, and 27% had received prior autologous

ABSTRACT SUMMARY Elevated Axicabtagene Ciloleucel (CAR-19) Expansion by Immunophenotyping Is Associated With Toxicity in Diffuse Large B-Cell Lymphoma

Twenty-two patients with aggressive lymphoma received axicabtagene ciloleucel at a single academic center (Abstract 576). Eight of the patients (36%) would have been ineligible for ZUMA-1. At day 28, the ORR was 86%, with a CR rate of 45%. Among 15 patients evaluable at 3 months, the ORR was 53%, including 7 patients with a CR and 1 with a PR. The median hospitalization duration was 13.5 days (range, 7-44 days). Eighteen patients (82%) required corticosteroid treatment. Twenty-one patients (95%) developed grade 1/2 cytokine release syndrome. There were no reports of cytokine release syndrome at grade 3 or higher. Neurotoxicity was observed in 14 patients (64%), including 6 patients (27%) with grade 3/4 events. Among the latter were 2 patients with grade 4 neurotoxicity, who also exhibited the highest amount of CART-cell expansion. Expansion of CART cells in the peripheral blood was associated with cytokine release syndrome and neurotoxicity, but not clinical response.

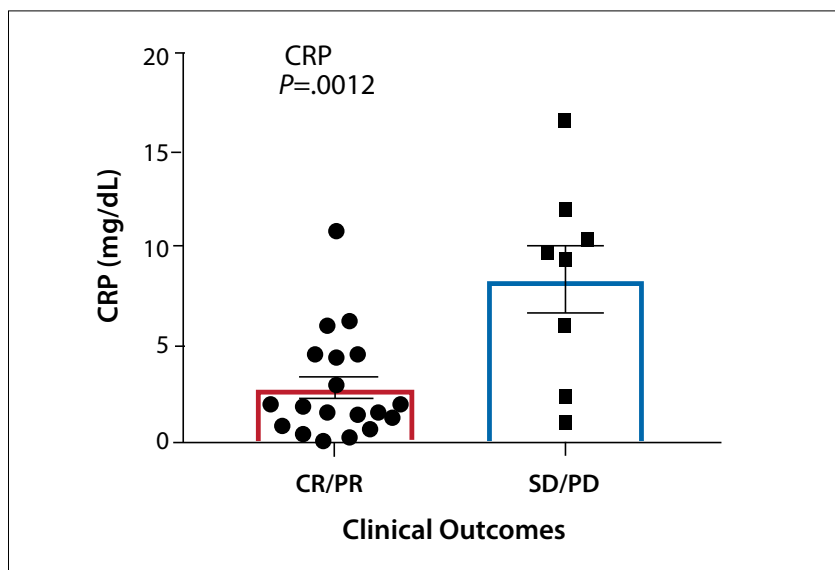


Figure 10. In a study of axicabtagene ciloleucel in patients with diffuse large B-cell lymphoma, those who achieved a complete response or partial response were more likely to have lower baseline levels of C-reactive protein. CR, complete response; CRP, C-reactive protein; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Faramand R et al. ASH abstract 95. *Blood*. 2018;132(suppl 1).²

stem cell transplant.

At day 30, the ORR was 70%, including a CR rate of 50%. At day 90, the ORR was 57% (12/21) and the CR rate was 46% (10/21).

Cytokine release syndrome of any grade was reported in 97% of

patients. Grade 3 or higher cytokine release syndrome occurred in 13%. The median time to onset of cytokine release syndrome was 4 days. Tocilizumab and corticosteroids were each used in 53% of patients. CAR T-cell-related encephalopathy syndrome of any grade

ABSTRACT SUMMARY Patient-Reported and Neurocognitive Outcomes in Patients Treated With Axicabtagene Ciloleucel

An observational study examined patient-reported outcomes and neurocognitive functioning within 90 days of treatment with axicabtagene ciloleucel (Abstract 2289). Patients at a single center who were scheduled to undergo axicabtagene ciloleucel infusion were recruited before administration of conditioning chemotherapy. They completed a questionnaire covering 20 symptoms linked to CAR T-cell therapy, as well as symptoms that were considered to be of concern to cancer patients. Outcomes were reported on days 0, 14, 30, 60, and 90. Among the 59 patients, 71% had DLBCL. Moderate-to-severe symptoms were most common on day 14, with the most frequent being fatigue (75%), decreased appetite (61%), dry mouth (55%), concentration problems (35%), constipation (30%), and headache (30%). Mental health quality of life improved significantly from baseline to day 90 ($P=.04$), but physical health quality of life remained stable ($P=.33$). Neurocognitive function was also stable from baseline through day 90 after infusion of axicabtagene ciloleucel ($P=.97$).

was reported in 80% of patients. This syndrome was grade 3 or higher in 37%. The CARTOX score was less than 7 in 53% of patients.⁴ The median time to onset of CAR T-cell-related encephalopathy syndrome was 6 days.

Baseline levels of CRP and ferritin were elevated in patients who

developed cytokine release syndrome or CAR T-cell-related encephalopathy syndrome of grade 3 or higher, compared with the rest of the study population ($P<.05$). Baseline levels of IL-6 were higher among patients who experienced cytokine release syndrome ($P=.03$) or CAR T-cell-related

encephalopathy syndrome ($P=.0038$) of grade 3 or higher. Baseline levels of angiopoietin were higher in patients who developed severe CAR T-cell-related encephalopathy syndrome ($P=.0078$). Patients who achieved a CR or PR were more likely to have lower baseline levels of CRP ($P=.0012$; Figure 10), ferritin ($P=.0077$), tumor necrosis factor ($P=.0023$), and IL-6 ($P=.0017$). Levels of catecholamines were elevated in patients with severe cytokine release syndrome ($P=.0011$).

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Outcomes of Patients With Large B-Cell Lymphomas and Progressive Disease Following CD19-Specific CAR T-Cell Therapy

In patients with relapsed or refractory large B-cell lymphoma, CD19-directed CAR T-cell therapy has demonstrated efficacy, with durable CRs in approximately 40%.¹⁻³ Among patients without a CR after CAR T-cell therapy, disease progression generally occurs within a few months. A study was conducted to describe outcomes in patients who developed progressive disease after CD19-specific CAR T-cell therapy.⁴ Bridging therapy was allowed in patients with active disease after leukapheresis and before the CAR T-cell infusion. Initial progressive disease was defined as progression at the first response assessment after the CAR

T-cell infusion. After infusion with CAR T cells, patients did not receive any protocol-specified treatment for their lymphoma. The primary analysis was overall survival after progressive disease. The study did not include information on CAR T-cell products, construction, or dosing.

Among 58 patients in the study, progressive disease was considered initial in 30 patients and delayed in 28 patients. The median time to progressive disease after CAR T-cell infusion was 29 days in patients with initial progressive disease vs 73 days in patients with delayed progressive disease. The patients' median age was 60 years

(range, 26-75 years). The most common histology was DLBCL (58.6%), followed by high-grade B-cell lymphoma (20.7%), transformed follicular lymphoma (15.5%), and PMBCL (5.2%). Most patients had an IPI of 2 or 3 (63.8%), and 15.5% had an IPI of 4 or 5. The median level of lactate dehydrogenase was 210 U/L (range, 111-2339 U/L). Characteristics were generally similar among patients with initial progressive disease vs those with delayed progressive disease. One difference was that patients with initial progression had a higher median level of lactate dehydrogenase at baseline ($P=.026$).

Among the 58 patients, the median overall survival after progressive disease was 5.3 months. Median overall survival was 3.75 months among patients with initial progression vs 13.42 months in those with delayed progression ($P=.038$). Twenty patients overall (34.5%) were treated with bridging therapy, including chemotherapy with or without corticosteroids (45.0%), corticosteroids only (25.0%), a novel or targeted agent with or without corticosteroids (25.0%), and intrathecal chemotherapy. The median overall survival was 3.16 months in patients who received bridging therapy vs 7.14 months in those who did not ($P=.37$). Among patients who received bridging therapy and developed initial progressive disease, the median overall survival was 2.34 months vs 13.55 months in patients without bridging therapy

who developed delayed progressive disease ($P=.19$). The median overall survival was 13.55 months in the 20 patients with no bridging therapy who developed delayed progressive disease vs 3.55 months in the other 38 patients ($P=.059$).

Forty-four patients (76%) went on to receive at least 1 subsequent therapy after progressive disease. The most common initial subsequent therapies included CAR T-cell therapy (14/44), a novel therapy (13/44), and chemotherapy with or without rituximab (7/44). Radiotherapy or inhibitors of programmed cell death protein 1 (PD-1) were administered to 4 patients each, and intrathecal chemotherapy or allogeneic stem cell transplant were administered to 1 patient each. The risk of death was reduced in patients treated with at least 1 therapy after progressive

disease (hazard ratio, 0.48; 95% CI, 0.234-0.99; $P=.0476$). Six patients enrolled in a clinical trial as their next line of therapy. Five patients eventually underwent an allogeneic stem cell transplant, and 2 were alive at the time of the study report.

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Highlights in CAR T-Cell Therapy in Lymphoma From the 60th American Society of Hematology Annual Meeting: Commentary

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The 60th American Society of Hematology (ASH) annual meeting had a number of remarkable abstracts that presented data in lymphoma patients treated with chimeric antigen receptor (CAR) T-cell therapy. Of particular interest were abstracts that highlighted data from patients treated outside of clinical trials with now standard-of-care CAR T-cell therapy, which demonstrated convincingly that the treatment is available and working in the real world.

Importantly, community oncologists should consider their patients for early referral for CAR T-cell therapy. They should expect that up to 40% of patients with refractory diffuse large B-cell lymphoma (DLBCL) will have durable and long-lasting remissions of 2 years and longer, with minimal long-term safety risks.

The CAR T-cell therapy axicabtagene ciloleucel is approved by the US Food and Drug Administration (FDA) for adult patients with relapsed/

refractory DLBCL, based on results from the ZUMA-1 trial (Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma).¹ I was a senior investigator in a real-world analysis of axicabtagene ciloleucel that was presented at the ASH meeting by Dr Loretta Nastoupil.² The co-first author was Dr Michael Jain. The study provided data on patients with aggressive B-cell lymphomas who underwent apheresis for the manufacture of axicabtagene

ciloleucel at 1 of 17 centers that formed an independent consortium. The study identified 295 patients who underwent apheresis prior to August 31, 2018. Among these patients, 274 received an infusion of axicabtagene ciloleucel by the data cutoff of October 31, 2018. The median follow-up duration was 3.9 months.

Remarkably, the percentage of patients who received CAR T-cell therapy was high, at 93%, and similar to the 91% who received axicabtagene ciloleucel infusion in the ZUMA-1 trial. The median time from leukapheresis to the start of conditioning chemotherapy was also similar to that in ZUMA-1, at 21.5 days. However, in stark contrast to ZUMA-1—in which no patient was allowed bridging therapy in the interval from apheresis to the start of conditioning chemotherapy and CAR T-cell infusion—in the real-world analysis, 55% of patients received some form of bridging therapy.

Baseline characteristics of the patients in the real-world analysis were somewhat similar to those of patients in ZUMA-1. Of note, 33% of the patients were 65 years or older, 75% had received 3 or more prior lines of therapy, and 35% had primary refractory disease. In a subset of 272 evaluable patients, 23% were double-hit or triple-hit according to fluorescence in situ hybridization (FISH), and 38% were double expressers by immunohistochemistry. There were several notable differences between the real-world population and patients in ZUMA-1. For example, 43% would not have met eligibility requirements for ZUMA-1 at the time of leukapheresis, for reasons such as low platelet count, active deep vein thrombosis or pulmonary embolism, prior anti-CD19 or CAR T-cell therapy, decreased renal function, history of central nervous system lymphoma or symptomatic effusion, decreased ejection fraction, and poor performance status. Despite the high percentage of patients who would not

have been eligible for ZUMA-1, the safety of the therapy appeared similar in both studies. In the real-world analysis, cytokine release syndrome of any grade occurred in 92% of patients, but it was grade 3 or higher in only 7%, comparing favorably with the 13% seen in the ZUMA-1 trial. The rate of grade 3 or higher neurotoxicity was also similar, at 33% in this series vs 31% in ZUMA-1.

Perhaps most importantly, the efficacy of axicabtagene ciloleucel when given as a standard-of-care therapy appeared similar to that described in the ZUMA-1 trial. At a landmark of day 90, 81% of patients had achieved an objective response and 57% had a complete response at some time prior. These rates were comparable to the overall objective response rate of 82% and the complete response rate of 54% in ZUMA-1.¹ There were several covariates associated with a lack of ongoing complete response at 3 months, including an ECOG performance status of 2 or higher, bulky disease (>10 cm), and failure to meet the eligibility criteria for ZUMA-1. However, the rates of complete response at 3 months continued to be favorable for these subgroups as compared with historical controls, indicating that all DLBCL patients who relapse after second-line therapy should at least be considered for axicabtagene ciloleucel therapy. I recommend that all community oncologists consider early referral, even at the time of first relapse, for consideration of CAR T-cell therapy or autologous stem cell transplant, depending upon the response to second-line therapy. Early referral is important considering the aggressive nature of refractory DLBCL and the lag time between vital organ testing and apheresis up until infusion of CAR T cells.

In conclusion, it appears that the safety and efficacy of standard-of-care axicabtagene ciloleucel in this real-world analysis were comparable to those in ZUMA-1, even though more than 40% of patients would not have

met the eligibility criteria for the clinical trial. An ongoing analysis is identifying predictors of ongoing response with axicabtagene ciloleucel.

Dr Caron Jacobson presented the results of a similar real-world analysis of axicabtagene ciloleucel from other centers not represented in the prior study.³ This analysis included 104 patients, with a median follow-up of 5.6 months. Eleven percent of the patients did not undergo infusion with axicabtagene ciloleucel. Among those who were infused, 71% had a response, including a complete response in 44%. Adverse events included grade 3 or higher cytokine release syndrome in 16%, and grade 3 or higher neurotoxicity in 39%. Again, these findings were comparable to those in the ZUMA-1 trial. Univariate analysis showed inferior outcomes in patients with poor performance status (an ECOG score of 2 to 4) or increased tumor bulk. Duration of response, progression-free survival, and overall survival were improved among patients with lower levels of C-reactive protein—a marker of inflammation—on day zero at the time of the infusion. Like the analysis by Dr Nastoupil,² this study demonstrated that axicabtagene ciloleucel can be successfully administered across multiple centers. It also showed that the use of bridging therapy among patients otherwise eligible for ZUMA-1 did not appear to improve outcomes or impact the rates of high-grade toxicities.

I was also fortunate to be a senior investigator in a retrospective real-world analysis by Dr Michael Jain, which provided some of the first data on the use of radiation therapy as a bridging agent while CAR T cells are being manufactured for standard-of-care administration.⁴ The 9 patients in this analysis had refractory disease as defined in the label for axicabtagene ciloleucel. The response to radiation therapy was assessed by local response at the site of the individual areas where the radiation was administered, and

most patients had stable disease as an initial response to the radiation. One patient had a complete response in the irradiated areas, while another developed progressive disease in these areas. Following CAR T-cell therapy, which was performed after the radiation, 6 of 8 patients (75%) had a partial response or a complete response at the localized area of radiation.

Importantly, radiation as a bridge to CAR T-cell therapy appeared safe. Any-grade cytokine release syndrome was reported in 94% of patients; the syndrome was grade 3 or higher in 16%, similar to the rates of severe toxicity related to CAR T-cell therapy reported in ZUMA-1.¹ This study showed that radiation may be used as a bridge for chemorefractory lymphoma patients who are awaiting manufacture of CAR T cells, even those with bulky masses or higher-risk disease. Further studies must be done to determine if there is an immunologic effect of radiation on CAR T-cell therapy.

Dr Dahlia Sano presented the results from a single-institution study that evaluated the outcomes of older patients with relapsed or refractory large-cell lymphoma treated with axicabtagene ciloleucel.⁵ The study demonstrated that response rates and survival were comparable between younger patients and those ages 65 years and older. Importantly, the safety was also comparable. The periods of hospitalization and days spent in the intensive care unit were similar between younger and older patients. Rates of tocilizumab use were also similar, but the use of corticosteroids was lower in elderly patients, at 30%, vs 52% in younger patients. This important study demonstrated that axicabtagene ciloleucel can be used safely in elderly patients with aggressive B-cell lymphomas.

Dr Natalie Grover presented results from an evaluation of patients in a phase 1b/2 trial of CD30-directed, CD28-costimulatory CAR T-cell therapy among adults with CD30-positive

lymphoma who required treatment after 2 prior lines of therapy.⁶ This CAR T-cell therapy had been previously tested in a feasibility trial, which showed that it could be administered safely without the use of conditioning chemotherapy, and it did induce some complete responses.⁷ This follow-up trial added conditioning chemotherapy to lymphodeplete patients prior to administration of CAR T-cell therapy and a phase 1 dose-escalation/dose-finding arm to identify a safe dose of CAR T cells in combination with lymphodepletion. There were no dose-limiting toxicities, and the phase 2 trial was opened with a dose of 2×10^8 CAR T cells/m². Twenty-four patients were evaluable by the data cut-off date: 22 had Hodgkin lymphoma and 2 had T-cell lymphoma. These patients were very heavily pretreated, with a median of 7.5 prior lines of therapy. Most had already received the CD30-targeted agent rituximab or checkpoint inhibitors. Patients underwent lymphodepletion with bendamustine at 90 mg/m² for 2 days. The addition of lymphodepletion demonstrated an increased expansion of CAR T cells compared with data from a trial that did not use lymphodepletion, and there were no dose-limiting toxicities.⁷ Lymphodepletion with bendamustine alone did not clearly increase the response rates, and in the second part of the trial, there was a switch to using bendamustine plus fludarabine as the regimen for conditioning chemotherapy. After this change, 12 of 14 evaluable patients treated with bendamustine plus fludarabine had a complete response, including 2 patients with a complete response that lasted longer than a year. A statistically significant difference in progression-free survival was seen between patients who received the combination of bendamustine and fludarabine (396 days) vs patients who received bendamustine alone (55 days). This finding is concordant with a report from the Seattle group showing that cyclophos-

phamide plus fludarabine was superior to cyclophosphamide alone when utilizing a CD19-directed CAR T-cell therapy,⁸ suggesting that conditioning chemotherapy is important to the efficacy of CAR T-cell therapy. The authors concluded that this approach had an acceptable safety profile. It is encouraging to know that CD30-directed CAR T cells may be useful for the treatment of Hodgkin lymphoma and T-cell lymphoma. Large trials will be needed to confirm efficacy.

Dr Sattva Neelapu presented results from long-term follow-up of the ZUMA-1 trial, of which I was the senior author and co-lead investigator.⁹ These results were simultaneously published in *The Lancet Oncology*.¹⁰ This long-term analysis confirmed the originally reported outcomes, showing an overall response rate of 83% and a complete response rate of 58%. Now at a median follow-up of 27.1 months and with all patients eligible for 2-year follow-up, the median overall survival was not reached, and 39% of patients maintained an ongoing response. This finding is remarkable because in patients with DLBCL, a durable response lasting 2 years after upfront chemotherapy or consolidative autologous transplant predicts for remission at 5 years and later.¹¹ This analysis therefore suggested that the lymphoma might not recur in many of these patients. Another key finding is that among patients in whom a single infusion of axicabtagene ciloleucel led to a partial response or complete response at 90 days after treatment, the chance for ongoing remission at 24 months was approximately 75%, suggesting that consolidative transplant is not necessary after CAR T-cell therapy to sustain remission. This long-term follow-up analysis identified only 4 additional serious adverse events, which were primarily infection-related and reversible. This study again highlights the finding that CAR T-cell therapy appears to induce

urable remissions in patients with aggressive B-cell lymphoma.

Disclosure

Dr Locke is a scientific advisor to Kite Pharma and Novartis. He is a consultant to Cellular Biomedicine Group, Inc.

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